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EFFECT OF DIISOPROPYL FLUOROPHOSPHATE ON GLYCOLYSIS IN MUSCULAR TISSUE

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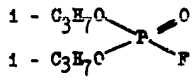
[Numbers in parentheses refer to the bibliography.]

Fluorine-substitution alkyl phosphates of the Lange type of esters have been a frequent object of consideration in postwar chemical and toxicological literature (1, 2).

The most studied representative of this group of materials is diisopropyl flucrophosphate (DFP), an extremely toxic compound with the express properties of a neurotoxin. A study of its influence on metabolism has revealed that even at extremely low concentrations it is able to inhibit cholinesterase activity. This, apparently is the reason for its toxic effect on the organism (3, 4).



The action of DFP on other enzymes has received but little attention, and the bits of data in literature are often not very conclusive. For example, it was indicated recently (5) that the glycolysis fermentation system in muscles is insensitive to the action of alkyl fluorophosphates. However, although the author states that he studied the action of alkyl fluorophosphate in concentration 0.002 M, he failed to introduce any experimental data to substantiate his assertion. It is not even clear as to whether the effect of DFP was studied or only the action of its dimethyl and diethyl homologues.

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The work here described, which included the study of the effect of diisopropyl fluorophosphate on glycolysis in muscular tissue, had already been completed when the reference above became known to us.

Method

We excised the muscles of rabbits under narcosis and, after freezing in liquid oxygen, pulverized them in a mortar. Approximately one gram of the fine powder obtained was placed in a previously weighed flask containing all the necessary supplements with a total volume of 10 milliliters. A second weighing confirmed the exact amount of the muscular tissue obtained. To determine the initial content of lactic acid, an albumin precipitant was added to one flask before introduction of the powdered tissue. The remaining specimens, with and without the supplements, were incubated at 38 decrees for 60 minutes. We determined the intensity of glycolysis by lactic acid accretion during the incubation period. We used the Friedemann-Cotonio-Shaffer iodometric method to determine the lactic acid count (6). Hexose diphosphate was obtained in accord with Ferimen's notes (7).

Results

In the first experimental series we were able to demonstrate that, in the concentrations used, DFP manifested a pronounced inhibitive action on the glycolitic activity of the muscular specimen. From the results of this series, found in Table 1, it is evident that the addition of DFP causes a certain reduction in lactic acid accretion during incubation. It was found that this inhibitive effect on glycolysis was directly related to the diisopropyl fluorophosphate concentration. Even a 0.001 M concentration -- half that used by Wood (5) -- brought about almost a two-thirds reduction of glycolytic activity in the muscular tissue.

Table 1. Effect of Diisopropyl Fluorophosphate in Glycolysis in Muscular Tissue Preparation

(incubation 60 min at 38°)

No	DFP Concentration in M/1	Lactic Acid Accretion During Incubation in mg %		Glycolytic Activity of Poisoned Preparation in % of Normal
		Without DFP	With DFP	
1	0.01	388	11	3
2	0.01	442	12	3
3	0.005	300	27	9
4	0.005	305	31	10
5	0.001	382	77	20
6	0.001	417	96	23
7	0.001	316	97	31
8	0.001	360	111	31
9	0.001	211	77	36
10	0.001	259	109	42

Aqueous solutions of DFP are easily hydrolyzed by the separation of a fluorine ion. The natural assumption then would be that the fluoride formed is the agent which disrupts the course of glycolysis. It is indeed necessary to note that in order to avoid or at least considerably reduce DFP hydrolysis, we used a distilled DFP preparation in every case, and prepared solutions of it as needed.

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On the basis of the numerous tests conducted on other occasions, we feel certain that sodium fluoride in a concentration of 0.001 M definitely hinders glycolysis. To ascertain whether DFP acts directly on glycolysis or whether its action depends solely on the fluoride formed during hydrolysis, we decided to study the effect of DFP on lactic acid formation not from the glycogen pre-existent in the muscular tissues, but from intermediate products of glycolysis, to be added to the specimens. We selected hexose diphosphate (GDP) for the intermediate product, and effected a comparative study of the action of DFP and NaF, the results of which appear in Table 2.

Table 2. Effect of Diisopropyl Fluorophosphate and Sodium Fluoride on Glycolysis in the Presence of Hexose Diphosphate

(incubation 60 min at 38°; hexose diphosphate, 25 mg per specimen)

No	Poison Added	Lactic Acid Accretion in mg % During Incubation				Lactic Acid Accretion Due to GDP	
		Without Poison		With Poison		Without Poison	With Poison
		Without GDP	With GDP	Without GDP	With GDP		
1	DFP-0.001 M	211	319	77	183	108	106
2		325	443	41	125	118	84
3		259	319	109	186	60	77
4		331	451	46	165	120	119
5	NaF-0.001 M	417	756	38	49	339	11
6		331	451	22	30	120	8
7		382	729	48	53	347	5
8		325	443	31	31	118	0

In these tests, the hexose diphosphate was placed in the flask prior to introduction of the muscular tissue. Consequently, the calculated amount of lactic acid was a total dependent upon the breaking down of both the natural glycogen and the added hexose diphosphate. By deducting the figures on the specimens without GDP from the results obtained it is possible to determine the amount of lactic acid formed through the added GDP.

Table 2 shows that the addition of GDP in every case produced excess lactic acid formation. However, this excess accretion fluctuated quite differently under the effect of diisopropyl fluorophosphate and sodium fluoride. The addition of DFP had practically no effect on the formation of lactic acid by hexose diphosphate; but sodium fluoride caused an almost complete cessation of the process.

It is known that in the presence of sodium fluoride, the glycolytic process ceases at the point of formation of 2-phosphoglyceric acid, which does not undergo further transformation. For this reason, it is natural that hexose diphosphate, as an earlier intermediate product, cannot be a source of lactic acid formation when sodium fluoride is present. On the other hand, diisopropyl fluorophosphate does not at all inhibit the transformation of hexose diphosphate into lactic acid and, consequently, has no effect on the subsequent course of glycolysis.

Thus, the inhibitive action of diisopropyl fluorophosphate on glycolysis is expressed in the disruption of certain of the stages prior to the formation of hexose diphosphate. The results obtained show that hexose diphosphate [sic] and sodium fluoride, as glycolytic poisons, have different points of application. The inhibitive action of diisopropyl fluorophosphate must be regarded not as dependent upon formation of the fluoride during hydrolysis, but as inherent in the structure of the whole molecule of this compound.

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Conclusion

Diisopropyl fluorophosphate (DFP) greatly inhibits glycolysis in muscular tissue. The inhibitive effect of DFP consists in disrupting the initial stages of glycolysis, prior to the formation of hexose diphosphate.

The effect of DFP on glycolysis is inherent in the structure of the whole molecule of this compound and does not depend on the fluoride which may be formed during the hydrolysis of DFP.

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